Remarks

Reconsideration and withdrawal of the rejection of claims, in view of the amendments and remarks herein, is respectfully requested. Claims 63-64, 67-68, 71-72, 75-76, 78-79, 81-82, and 92 are canceled. Claims 77 and 83-87 are allowed. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in continuation application of the above-referenced application. Claims 65, 69, 73, 77, 80, and 83-91 are pending in the application.

The Examiner is thanked for the courtesies extended to Applicant's Representative in the telephonic conversation on July 14, 2004.

The Examiner rejected claims 63-65, 67-69, 71-73, and 75-83 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of inhibiting leukocyte migration by administration to a mammal of an effective amount of SEQ ID NO:1, 7, 14, 38, 40-44, 65-68, 72-74, and certain reverse D sequences, allegedly does not reasonably provide enablement for a method of preventing or inhibiting an indication associated with leukocyte recruitment or migration by administration of the peptides. This rejection is respectfully traversed.

Claims 88-92 are not mentioned in the rejection, however, as the §112(1) rejection is the only rejection and PTOL-326 indicated that claims 88-92 are rejected, claims 88-92 are apparently rejected under § 112(1).

Specifically, the Examiner asserts that Applicant has provided insufficient guidance to 1) enable one of ordinary skill in the art to determine, without undue experimentation, the risk factors for indications associated with leukocyte migration or recruitment and so how to prevent those indications, and 2) enable one of ordinary skill in the art, without undue experimentation, to inhibit indications by administering peptidic compounds due to the unpredictability of animal models and pharmaceutical therapies.

The Examiner is respectfully requested to consider that the pending claims do not recite "indication."

The allowed claims are directed to: 1) a method of inhibiting leukocyte recruitment at a preselected physiological site, comprising: administering to a mammal a dosage form comprising

an effective amount of Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln (SEQ ID NO:14), wherein the dosage form is linked to a site targeting moiety (claim 77); 2) a method of inhibiting leukocyte recruitment at a preselected physiological site, comprising: administering to a mammal a dosage form comprising an effective amount of CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys, wherein the dosage form is linked to a site targeting moiety (claim 83); 3) a method of inhibiting leukocyte migration or recruitment comprising: administering to a mammal an effective amount of Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln (SEQ ID NO:14) or CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys (claim 84); and 4) a method of inhibiting leukocyte migration or recruitment, comprising: administering to a mammal an effective amount of a peptide comprising no more than 30 amino acid residues, which peptide comprises SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:73, or SEQ ID NO:74 (claim 86).

The pending rejected claims are directed to: 1) a method of preventing or inhibiting leukocyte recruitment at a preselected physiological site, comprising: administering to a mammal a dosage form comprising an effective amount of Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln (SEQ ID NO:14), wherein the dosage form is linked to a site targeting moiety (claim 65); 2) a method of preventing or inhibiting leukocyte recruitment at a preselected physiological site, comprising: administering to a mammal a dosage form comprising an effective amount of a peptide comprising no more than 30 amino acid residues, which peptide comprises SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:27, reverse D Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln, reverse D Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys, or reverse D Glu-Ile-Cys-Ala-Asp-Pro-Lys-Gln-Lys-Trp-Val-Gln-Cys, wherein the dosage form is linked to a site targeting moiety (claim 69); 3) a method of preventing or inhibiting leukocyte recruitment at a preselected physiological site, comprising: administering to a mammal a dosage form comprising an effective amount of CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys, wherein the dosage form is linked to a site targeting moiety (claim 73); 4)

a method of preventing or inhibiting leukocyte migration or recruitment comprising: administering to a mammal an effective amount of Glu-Ile-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln (SEQ ID NO:14) or CRD-Cys-Leu-Asp-Pro-Lys-Gln-Lys-Trp-Ile-Gln-Cys (claim 88); and 5) a method of preventing or inhibiting leukocyte migration or recruitment, comprising: administering to a mammal an effective amount of a peptide comprising no more than 30 amino acid residues, which peptide comprises SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:73, or SEQ ID NO:74 (claim 90).

Generally, the only difference between the allowed claims and the pending rejected claims is that the pending rejected claims are directed to the use of the same compounds to "prevent" leukocyte migration or recruitment.

As discussed in the Rule 132 Declaration of Dr. David Grainger submitted with the Amendment filed on September 25, 2003, the diseases encompassed by the claims have an inflammatory component (paragraph 4 of the Declaration), and that since chemokines are central regulators of leukocyte recruitment or migration, altering chemokine function affects leukocyte recruitment or migration dynamics and hence affects the progression of the disease state (paragraph 10 of the Declaration). For instance, Table 1 of Elson et al. (Gastroenterology, 109:1344 (1995)) (of record) summarizes components contributing to inflammatory bowel diseases, including regulatory T cells, T cell cytokines, B cells, neutrophils, mast cells and phagocytes. Karpus et al. (J. Immunol., 155:5003 (1995)) (of record) notes that experimental autoimmune encephalitis is a $CD4^+$ T cell mediated inflammatory disease that serves as a model for multiple sclerosis, and that the chemokine MIP-1α plays a role in the pathogenesis of that disease. U.S. Patent No. 5,571,713 (of record) discloses that restenosis is often caused by a process in which monocytes and macrophage accumulate at areas of injury or inflammation, and may be treated by antisense MCP-1 oligonucleotides (column 1, lines 53-67 and column 2, lines 58-64). Ono et al. (Lab. Investig., 79:195 (1999)) (of record) relate that MCP-1 expression is upregulated after myocardial ischemia and that intravenous administration of anti-MCP-1 antibodies reduced infarct size and infiltration of macrophage (abstract). Similarly, MCP-1 is

likely a molecular signal for the macrophage response to hypoxic-ischemia injury in the brain (see, for instance, Ivacko et al., J. Cerebral. Blood Flow Meta, 17:759 (1997)) (of record).

Leukocyte infiltration is also a feature of uveitis, and certain chemokines are upregulated in patients with idiopathic acute anterior ureitis (Verma et al., Curr. Eye Res., 16:1202 (1997)) (of record). Further, data presented in Marra et al. (Am. J. Path., 152:423 (1998)) (of record) support the position that MCP-1 secretion contributes to the formation and maintenance of the inflammatory infiltrate observed during chronic liver disease. In addition, pathogens including viruses, bacteria and fungi, are well-known to induce an inflammatory response.

Accordingly, numerous diseases are recognized as having an inflammatory component.

Moreover, it is Applicant's position that it is well within the skill of the art worker to determine whether an individual is at risk of a particular disorder. For example, risk factors for asthma (Businco et al., Ped. Pulm. Supple., 16:19 (1997)); psoriasis (Naldi et al., Br. J. Derma., 135:858 (1996)); nephritis (Jin et al., Nephron., 73:390 (1996)); atherosclerosis (Spence et al., Baillieres Clin. Neurol., 4:191 (1995)); Alzheimer's disease (Frecker et al., Can. J. Neurol. Sci., 21:112 (1994)); multiple sclerosis (Luchinetti et al., Neurology, 49:1413 (1997)); diabetes (Rewers et al., Diabetologia, 39:809 (1996)); and osteoporosis (Marone et al., Rev. Paul. Med., 115:1590 (1997)) are known (all of record).

In this regard, the Examiner is also requested to reconsider documents provided with the Amendment submitted on September 25, 2003. For instance, Rewers et al. (Diabetologia, 39:809 (1996)) (of record) disclose that autoimmunity causing insulin-dependent diabetes mellitus (IDDM) begins in early childhood due to interactions between genes and unknown environmental factors (abstract). Rewers et al. identified HLA markers associated with IDDM, and concluded that large-scale newborn screening for genes associated with IDDM was feasible and that such a screening could provide for future routine prediction and prevention of IDDM (abstract). Businco et al. (Ped. Pulm. Supple., 16:19 (1997)) (of record) disclose that atopic dermatitis (AD) often preceeds asthma (page 19). Businco et al. disclose that asthma prevention in children with AD involves a prospective follow up of atopic sensitization or disease, and conclude that primary prevention of AD by dietary manipulation and prevention of respiratory allergies by environmental measure and pharmacological treatment is warranted (page 20). Jin et al. (Nephron, 73:390 (1996)) (of record) disclose that mutations at the complement 4 gene and

certain HLA alleles may be risk factors for IgA nephropathy and Henoch-Schöelein nephritis, and Lucchinetti et al. (Neurology, 49:1413 (1997)) (of record) disclose that bilateral sequential or recurrent optic neuritis is a risk factor for developing multiple sclerosis.

As also discussed in the Rule 132 Declaration, there is substantial evidence that an agent of the invention can be employed prophylactically (paragraph 11 of the Declaration), e.g., that administration of the agent can substantially prevent an indication associated with leukocyte migration or recruitment. In this regard, the Examiner is respectfully requested to consider Example 9 in the specification. Rats were administered (intravenous or subcutaneous) an agent of the invention prior to contact with LPS and MCP-1 or MCP-1. In this dermal inflammation model, the administered agent significantly reduced the inflammatory response to LPS and MCP-1 or MCP-1. Thus, individuals at risk of acute dermal hypersensitivity reactions, e.g., individuals at risk of dermal contact hypersensitivity to an allergen such as house dust mites or pollen as a result of prior exposure to the allergen, may be benefited by administration of the agents of the invention. Thus, the specification discloses the use of an agent of the invention to prevent an inflammatory response in a mammal.

Clearly, it is within the skill in the art to identify an individual at risk of leukocyte migration or recruitment and choose to treat that individual prophylactically.

With respect to "predictability or lack thereof" of pharmaceutical therapies and animal models, the "predictability or lack thereof" refers to the ability of one skilled in the art to extrapolate disclosed or known results to the claimed invention. M.P.E.P. § 2164.03. The Examiner is reminded that data from *in vitro* or animal testing is generally sufficient to support utility, and that human clinical data is not required. M.P.E.P. § 2107.03 (clinical data is not required to satisfy the enablement requirement for pharmaceuticals and methods of medical treatment). The standard is that the evidence provided by Applicant be convincing to one of skill in the art that the disclosed agents are useful for the claimed method. In re Brandstadter, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973) and M.P.E.P. § 2164.05.

In this regard, the Examiner is respectfully requested to consider Applicant's detailed disclosure. The specification provides exemplary *in vitro* and *in vivo* assays to determine whether a particular chemokine peptide, e.g., SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID

NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74 or SEQ ID NO:11, a variant or a derivative thereof, e.g., a CRD derivative, inhibits or reduces a chemokine-induced activity (page 50, lines 16-25). These assays include *in vitro* assays (see page 50, line 27-page 52, line 28) which detect whether an agent inhibits the chemokine-induced chemotaxis of a variety of cell types (e.g., neutrophils, monocytes, eosinophils, mast cells, platelets or lymphocytes; page 52, lines 1-2), inhibits the release of enzymes from certain cells (such as N-acetyl-β-D-glucosamidase from monocytes or elastase from neutrophils; page 53, lines 2-13), changes the concentration of cytosolic free Ca^{2+} in various cell types (monocytes, eosinophils, neutrophils; page 53, line 15-page 54, line 18), inhibits binding to a chemokine receptor and/or displaces bound chemokine (page 54, line 20-page 55, line 27), and inhibits the co-mitogenic activity of a chemokine (page 56, lines 14-20).

Example 1 discloses the use of an *in vitro* chemotaxis assay, i.e., the inhibition of chemokine-induced THP-1 (a monocytic cell line) migration, to identify regions of human MCP-1 (hMCP1) falling within the scope of the invention, e.g., SEQ ID NO:1. Example 4 describes that a CRD peptide variant of MCP-1 inhibited MCP-1-induced THP-1 migration e.g., CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83). Table 2 shows the inhibition by a MCP-1 chemokine peptide (SEQ ID NO:1) (claims 67-70 and 78-80) of the MCP-1-, MIP1α-, IL8- and SDF-1α-induced migration of THP-1 cells and primary human monocytes. Table 4 shows ED_{50} data for four chemokines (MCP-1, MIP1α, IL8 and SDF-1α) and selected peptides, e.g., SEQ ID NO:1, SEQ ID NO:7, and SEQ ID NO:14 (claims 63-66 and 75-77), which include variants of MCP-1 chemokine peptide, e.g., one variant peptide of human MCP-1 chemokine peptide (the variant is designated $Leu_4Ser_7Ile_{11}$peptide3(1-12)[MCP-1]) has amino acid substitutions at positions 4, 7 and 11 relative to the sequence of a 12 amino acid peptide of human MCP-1 designated peptide 3(1-12)[MCP-1], and another variant (referred to as $Ser_7Glu_8Glu_9$peptide3(1-12)[MCP-1]) has substitutions at positions 7, 8 and 9 relative to peptide 3(1-12)[MCP-1]. Thus, a particular chemokine peptide can inhibit the activity of more than one chemokine.

Table 4 also includes data from three chemokine peptides having three amino acid residues, one of which is a tripeptide from MIP-1α. Some of the peptides described in Table 4 were found to be pan-chemokine inhibitors, while others showed selectivity for certain groups of

chemokines, i.e., selectivity for CC or CXC chemokines. Example 6 discloses additional experiments for tripeptides of the invention. Thus, the tripeptide WVQ, a sequence found in the carboxy-terminal half of MCP-1, MCP-3, MIP-1α, MIP-1β, RANTES, eotaxin and IL8 (see SEQ ID Nos:1, 7, 40, 42, 43, 44, and 66), inhibited all four chemokines tested, while tripeptide KQK, another sequence found in the carboxy-terminal half of MCP-1, was specific for MCP-1 (versus MIP-1α, IL8 or SDF-1α). It is disclosed that the corresponding tripeptides for MIP-1α (SEE, see SEQ ID NO:42), SDF-1 (KLK, see SEQ ID NO:38), and IL8 (KEN, see SEQ ID NO:40) were each specific for the cognate chemokine.

It is further disclosed that the efficacy of a peptide of the invention in an animal model may be assessed by clinical parameters specific for the particular model or by general parameters such as the extent of inflammation or cellular infiltration into affected tissues (page 66, lines 15-16). For instance, in a murine endotoxemia model (Example 10), the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83) to mice resulted in a dose-dependent decrease in serum TNF-α. In a murine asthma model (Example 11), the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys (claims 71-74 and 81-83) to mice resulted in the absence of inflammatory infiltrates in the lung (page 164, lines 15-17 and page 165, lines 18-19). Example 9 discloses the activity of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys in a rat dermal inflammation model (see also Example 6 in PCT/US00/00821, where it is disclosed that CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys abolished MCP-1 induced recruitment of monocytes/macrophage), and PCT/US00/00821 discloses the activity of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys in a rat ischemia/reperfusion model (i.e., the administration of CRD-Cys-Leu-Asp-Pro-Lys-Trp-Ile-Gln-Cys resulted in a complete suppression of neutrophil accumulation).

Thus, based on the extensive disclosure in Applicant's specification including the *in vitro* and *in vivo* results therein, one of ordinary skill in the art could reasonably predict that chemokine peptides, variants or derivatives thereof, would be useful for preventing or inhibiting an aberrant or pathological inflammatory response.

Thus, Applicant has fully enabled the claimed invention. Accordingly, withdrawal of the § 112(1) rejection is appropriate and is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 2nd day of August, 2004.

Dawn M. Poole _____
Name

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